EXHIBIT 103

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Glutamate-induced Hyperactivity of NMDA ion channel in Postmortem Alzheimer's Disease Brains

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Abstract

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Objectives The N-Methyl-D-Aspartate (NMDA) receptor may be adversely affected in Alzheimer's Disease (AD) brains due to neurodegeneration. We report ^{3}H-MK801 autoradiographic studies in postmortem AD brains of the NMDA receptor ion-channel activity using glutamate (GLU), glycine (GLY), GLY site agonist serine (SER) and partial agonist 1-amino cyclopropane carboxylic acid (ACC).

Methods Human postmortem frontal cortex (FC) brain sections (AD, n=6, age 82-90, SP Stage C and controls (CL), n=6; age 85-88 SP Stage 0-A) were obtained from Banner Health and sliced (10 mm) using a Leica cryotome. Adjacent brain slices were incubated in 10 mM GLU, GLY, ACC, or SER, or GLU combinations thereof in 5mM Tris/pH 7.4 buffer and ^{3}H-MK801 (0.017mCi/cc) at 37°^{C} for 2 hr. Non-specific binding was measured using standard MK-801 (10 mM). Using the Optiquant program, regions of interest were drawn and digital light units/mm^{2} (DLU/mm^{2}) were used to quantify the percentage change in ^{3}H-MK801.

Results At baseline, AD FC was 1.7 times higher than CL. Added GLU showed a 1.4 fold increase in CL while AD FC showed a 2.3-fold increase compared to baseline. Thus, in the presence of GLU, AD FC increased significantly

(3.5 fold) compared to CL. In the presence of GLY and SER, CL showed a greater increase in binding (>2 fold) compared to AD. However, this difference in GLY and SER was suppressed in the added presence of GLU. ACC had similar effects as GLU (2.6 fold compared to CL). These results indicate a significant increase in GLU-induced ^{3}H-MK801 binding in AD brains, while little effect was seen in the presence of GLY, suggesting an anomalous GLY site in AD.

Conclusions Our preliminary results indicate that NMDA receptor activity is increased significantly in AD brains in the presence of GLU. Although NMDA ion-channel blocker, memantine, is used therapeutically in advanced AD, our findings suggest that diagnostic and therapeutic targeting of the ion-channel, GLU site, and GLY site may be appropriate in further refining diagnosis and treatment of mild to severe AD.

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